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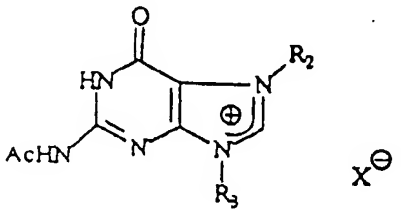

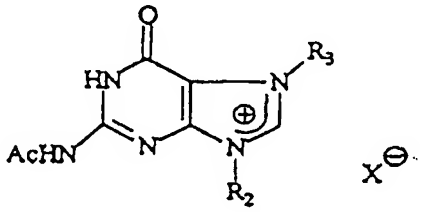

(57) Abstract

The invention relates to a new process for the preparation of alkyl substituted purine derivatives, especially of N7 and N9 alkyl derivatives of purine, and to novel compounds, namely N7 alkyl derivatives of purine endowed with a potential biological, e.g. antiviral or antitumoural activity. This new process enables the regioselective coupling of a specific alkyl group in 7 or 9 position of purine.

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ANTIVIRAL ALKYL SUBSTITUTED PURINE DERIVATIVES AND THEIR PREPARATION

The invention relates to a new process for the preparation of alkyl substituted purine derivatives, especially of N7 and N9 alkyl derivatives of purine, and to novel compounds, namely N7 alkyl derivatives of purine endowed with a potential biological, e.g. antiviral or antitumoural activity. This new process enables the regioselective coupling of a specific alkyl group in 7 or 9 position of purine.

Purine derivatives, in majority substituted in 9 position represent a plurality of important active substances endowed with antiviral activity. *Inter alia,* there are indicated: aciclovir, ganciclovir, and famciclovir and the like, which are still being researched. Recently, promising biological results for N7-substituted 2-amino purine possessing an acyclic component characteristic for ganciclovir (EP-A 448 006, EP-A 452 680), enhanced the palette of interesting active substances. Purine derivatives are usually prepared by coupling the side chain to the basic purine base. The basic problem and challenge are therefore an appropriate choice of the starting base (raw material), enabling the selective introduction of the selected side chain at the desired site, namely the N7 or N9 position.

Regioselective alkylation of guanine is, of course, no trivial problem. At first, the N1 and N3 positions have to be protected or deactivated. The coupling to the N7 position is a kinetically controlled process, whilst the N9 substituted derivatives are thermodinamically more stable. The final ratio between said products is also especially dependent on the substituent in C6 position (Nucleosides & Nucleotides, **8**, 225, 1989).

Provided, that owing to economic reasons the choice of the starting substances is concentrated on low-priced naturally obtained derivatives, easily available by industrial fermentation, to say guanosine and *via* said substance guanine, a serious problem is envisaged. Martin *et al.* have as late as 1983 isolated a mixture of N7 and N9 substituted compounds when using diacetyl guanine (J. Med. Chem., **26**, 559, 1983). The same applies to the penciclovir synthesis (Chinese J. Chem., **9**, 536, 1991).

It should be now mentioned, that the majority of academic work in the search for novel purine derivatives has been performed with 2-amino-6-chloro purine. By various means it was succeeded to enhance the ratio of the yields of individual derivatives N9 : N7 to values as high as 40 : 1. The condensation, however, was not selective. It also should be noted at this occasion, that 2-amino-6-chloro purine represents a high-priced mutageneous compound. (Tetrahedron Lett.; **33**, 469, 1992). We intentionally refrained from using it.

Last but not least, there was surprisingly established the outstanding biological activity of purine analogs possessing an acyclic component bound in position N7 (EP-A 448 006, 542 680). This fact is a further incentive in the search for general solutions in the selective coupling to the desired N7 and N9 positions. The first successful results were achieved by means of the N-triacetyl glyoxal derivative of guanine (US Patent 4,701,526; Acta Chem. Scan. B, **41**, 564, 1987); they succeeded in the selective binding of the alkyl group to the 7 position, however, with a poor yield (J. Het. Chem. **23**, 625, 1986).

For this reason, the very use of alkyl chains in the substitution of purine resulted in the need for a new process.

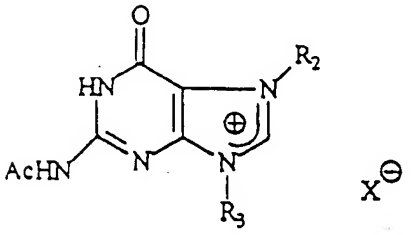
The object of this invention is a new, regioselective process for the preparation of alkyl substituted purine derivatives, specifically N7 or N9 alkyl purine derivatives, starting from 7- or 9- benzyl guanine.

A further object of this invention are N7 alkyl purine derivatives, that are novel compounds endowed with a potential biological, e.g. antiviral or antitumoural activity.

The solution of the above discussed problems, chosen by the present inventors, was the synthesis route characterized by the protection of the imidazole moiety of the guanine molecule possessing a benzyl group in 7 position or in 9 position dependent on the desired site of the substituent binding. The benzyl group may introduced in 7 position *via* the native nucleoside (guanosine) obtained by fermentation in a simple manner. (P. Brookes et al., J. Chem. Soc. (C) 2026, 1968 and P.K. Bridson *et al.*; Synthetic Commun.; 20, 2459, 1990). The protection of a specific site means, of course, the possibility of performing a selective condensation to the remaining active 7 or 9 position.

In the continuation of the reaction, the release of the protecting group located at the second nitrogen atom of the imidazole moiety of the molecule yields the desired compound in a regioselective way. In this manner, we also succeeded in the preparation of 9-benzyl guanine, namely from 7-benzyl guanine; the latter was used for further research. We also disclose a process for the preparation of famciclovir *via* the intermediate penciclovir obtained in conformance with the claimed process starting from 7-benzyl guanine.

According to this invention are obtained compounds of the formula 4 or 5:



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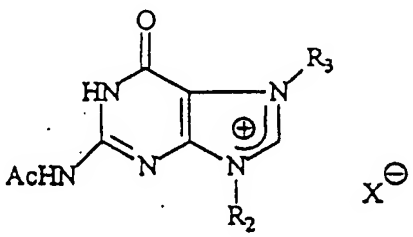


5

wherein:

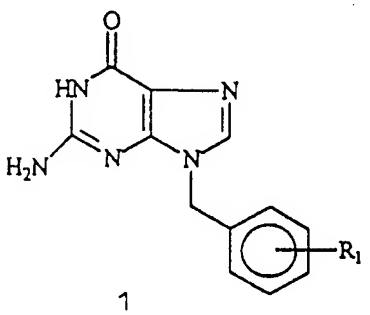
Ac represents acetyl,

R_2 represents a C_1-C_{12} linear or branched, saturated or unsaturated alkyl group, that may contain a 3-7 membered ring in the molecule, and also an ether, thioether, acetal, thioacetal, lactone, thiolactone, mono- or diacyl group, phosphorylmethoxy, phosphorylethoxy and phosphate groups,

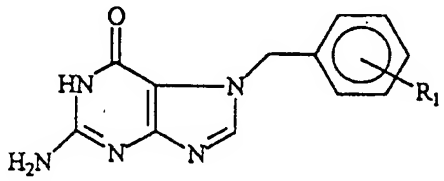
R_3 represents ring substituted p-methoxy, p-nitro, p-methyl benzyl groups,

X represents chloro, bromo, iodo, p-toluene sulphonic groups or mesyloxy groups;

by the reaction of the compound represented by the formula 1 or 2



1



2

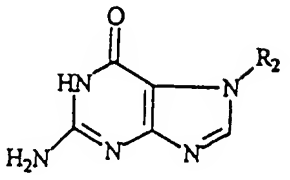
wherein R_1 represents hydrogen, a C_1-C_6 alkyl group, a C_1-C_{16} alkoxy group, a hydroxy group, a nitro group, an amino group, fluoro, chloro, bromo or iodo,

with the compound representing the desired substituent (chain) with the reactive removable group, represented by the formula 3

$$R_2X \qquad 3$$

wherein X and R_2 have the above meanings.

According to this invention are prepared 9- and 7-substituted purine derivatives represented by the formula 6 or 7



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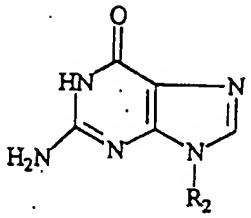
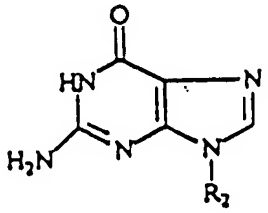


7

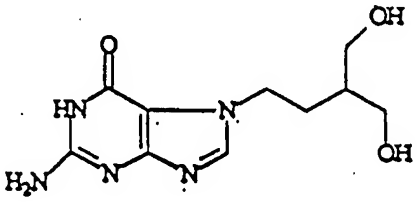
wherein R_2 has the above meanings,

by hydrogenation of the above compounds of formulae 4 and 5.

This invention discloses the preferred example of the synthesis of penciclovir



and the N7 isomer thereof represented by the formula 10



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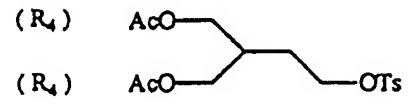
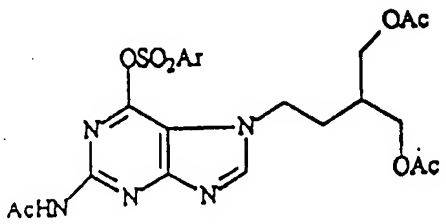
In the preparation of the above compounds the chain R_2X is represented by the formula 9



9

wherein R_4 represents a C_1-C_8 acyl group, a C_1-C_{10} alkyl group or a C_7-C_{22} arylalkyl group.

The claimed process comprises the deoxygenation of the compounds of formulae 6 and 7 *via* the O6-sulphonylated intermediates of formulae 11 and 12



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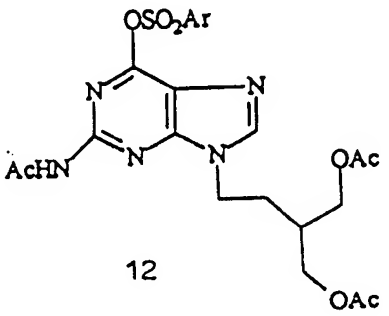


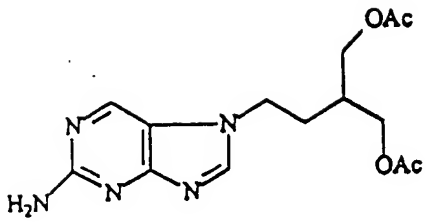
12

wherein

Ac represents acetyl,

Ar represents 2,4,6-$^{i}Pr_3C_6H_2$-, 2,4,6-$Me_3C_6H_2$-, 4-MeC_6H_4-, 4-FC_6H_4-,

into the famciclovir of the formula 14 and the isomer thereof of the formula 13



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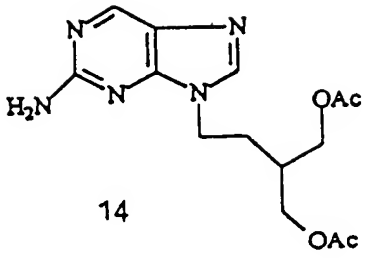


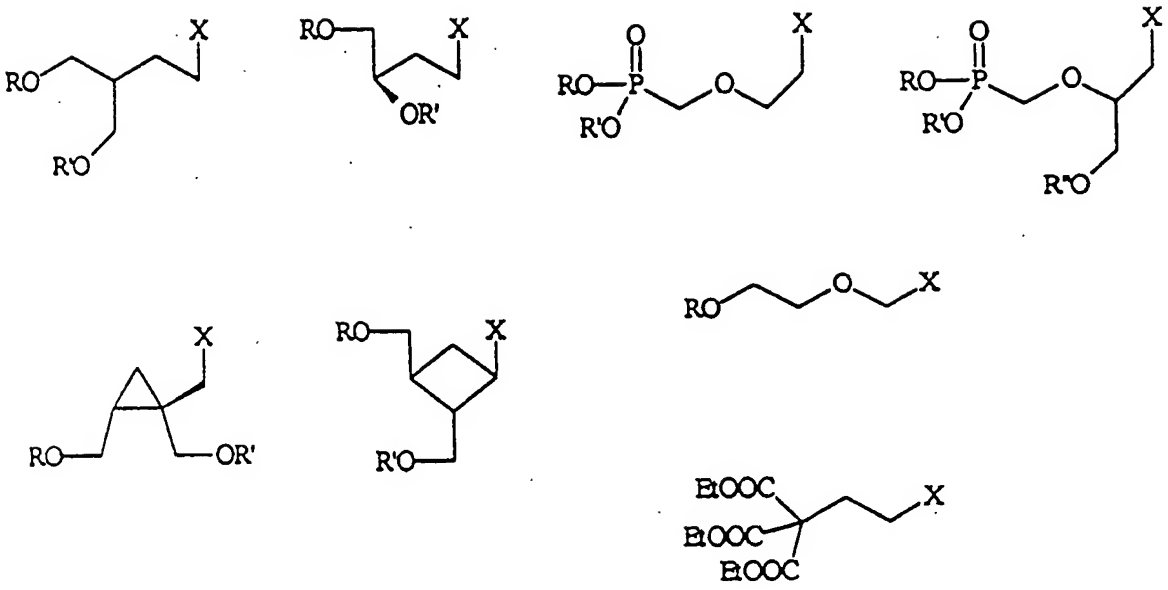
14

wherein Ac has the above meaning.

The starting substances used in the claimed process, to say the substituted N7-benzyl derivatives, may be obtained starting from purine nucleosides and the latter converted by hydrogenation *via* the intermediate of the formula 4 (R_3 = benzyl) into 9-benzyl guanine.

The compound of the formula 3 in conformance with this invention possesses a removable group, such as chloro, bromo, iodo, tozyl or mezyl groups, in the above mentioned linear or branched chain. In this invention the alkyl group represents a side chain characteristic for potentially bioactive nucleoside active substances, and is bound to the purine ring. The product of this composition has antiviral or antitumoural properties. The reaction is preferably characterized by the following substituents without, however, limiting its scope.

In the following formulae R, R' and R'' represent acetyl, benzoyl, benzyl or other standard protecting groups, and X has the same meanings as mentioned in the description of formulae 4 and 5.



The above mentioned compounds, to say the N-substituted derivatives, are known active substances. On the other hand, the N7-substituted derivatives are novel compounds.

The condensation reaction is performed in organic solvents, such as DMF, DMSO, 1-methyl-2-pyrrolidone, preferably in 1-methyl-2-pyrrolidone and at a temperature of 80 to 120 °C and is terminated within a few hours. The excess of the side chain (20 to 50%) is needed to improve the yield.

The compounds of formulae 4 and 5 are novel compounds, with the exception of the compounds disclosed in EP-A 728757 A.

The compounds of formulae 4 and 5 are obtained according to the above process, usually form salts. In the case, that the salt is not precipitating the debenzylation (hydrogenation) reaction may be performed on the crude product. Upon removal of the benzyl group the desired intermediates 6 and 7 are obtained. Conventional methods may be applied, such as the reduction in the presence of the palladium catalyst under hydrogen, or by means of formic acid or ammonium formate in standard solvents.

In this manner the claimed invention discloses and enables the regioselective preparation of alkylated purine derivatives directly from guanosine possesing substituents in position 9. The 9-substituted derivatives are applicable as medicines. The novel 7-substituted isomers, especially after the deoxygenation into 2-amino-7-alkil compounds represent a novel series of compounds endowed with potential biological activity e.g. an antiviral or an antitumoural activity.

The claim invention is illustrated by the following working Examples, without limiting its scope in any way.

Synthesis Example 1

7-Benzylguanine

Guanosine (56.6 g; 0.2 mole) was suspended in DMSO (150 mL) with stirring. The suspension was stirred for 20 min and then benzyl bromide (13 mL; 0.11 mole) was added. The reaction mixture was stirred at room temperature for 24 hours, and the resulting solution was then transferred to a beaker. 10% HCl (250 mL) was then added, and the mixture heated at 70° C for 2 hours, then cooled and filtered. The crystalline solid was washed with cold water, suspended in water and neutralized by addition of 6 M NaOH. The precipitate was filtered, washed with water and dried *in vacuo* at 120° C to yield 41 g (85%) of 7-benzylguanine in a powder form. This material can be used without further purification: m.p.> 360° C;

^{1}H NMR (DMSO-d_6) δ 8.07(1H,s,); 7.27-7.36(5H,m); 6.13 (2H,br.s); 5.41 (2H, s).

Synthesis Example 2

N^2-Acetyl-7-benzylguanine

7-Benzylguanine (9.65 g; 0.04 mole) was suspended in 1-methyl-2-pyrrolidone (40 mL) and then acetic anhydride (5.7 mL;0.06 mole) was added. The resulting suspension was heated with stirring at 150° C for 1 hour. The solvent was removed and the residue suspended in ethyl acetate (50 ml) and filtered. The resulting solid was washed with acetone (10 mL) to yield a white powder (10.5;93%); m.p.236-238° C;

MS (FAB) m/e =284 (MH^+, 100%); UV (H_2O, pH =6.4) λ_{max} =266 nm (ε =14.500); HRMS for $C_{14}H_{13}N_5O_2$ calc. 283.107, found 283.107; ^{1}H NMR (DMSO-d_6) δ 12.11 (1H, br.s), 11.58 (1H,s) ,8.35 (1H, s),7.31-7.35 (5H,m) , 5.51 (2H,s),2.15 (3H,s).

Synthesis Example 3

7,9-Dibenzyl-N^2-acetylguaninium bromide

Benzyl bromide (3.3 mL, 0.03 mole) was added to the suspension of N^2-acetyl-7-benzylguanine (5.6 g, 0.020 mole) in 1-methyl-2-pyrrolidone. The reaction mixture was heated with stirring at 120° C for 2 hours, then poured still hot into ETA (150 mL) and stirred for 1 hour. The resulting solid was filtered and washed with acetone (10 mL) and after drying yielded 7,9-dibenzyl-N^2-acetylguaninium bromide (8.1 g, 90%);

MS (EI) m/e = 373 (M-HBr, 60%), HRMS for $C_{21}H_{20}N_5O_2Br$-HBr calc. 373.154, found 373.155; ^{1}H NMR δ 12.61 (1H, br.s), 12.14 (1H, s), 9.83 (1H,s), 7.38-7.52 (10H, m), 5.71 (2H, s) 5.50 (2H, s), 2.22 (3H,s).

Guanine (4.53 g, 0.03 mole) was suspended in 1-methyl-2-pyrrolidone (50 mL), Ac_2O (7.3 mL, 0.07 mole)was added and the reaction mixture stirred for 4 hours at 150° C. The solvent was removed, and fresh 1-methyl-2-pyrrolidone and benzyl bromide (7.2 ml, 0.06 mole) were added subsequently. The reaction mixture was then heated for 2 more hours at 120° C. The dark coloured solution was transferred into hot ETA (250 mL) with stirring . After sufficient cooling of the mixture, salt began to separate, which was after 1 hour period collected on a filter and washed with acetone (2x 25 ml). A slightly coloured salt was obtained after drying *in vacuo*. (12.6 g, 92%). This material was used without further purification.

Synthesis Example 4

9-Benzylguanine

10% Pd/C (1.2 g) was added to a solution containing 7,9-dibenzyl-N^2-acetyl guaninium bromide (11.5 g, 0.025 mole) and ammonium formate (4.4 g, 0.07 mole) in methanol (230 ml). The mixture was heated with stirring at reflux for 4 hours, filtered hot and the catalyst washed with hot methanol. Water ammonia (20 mL) was added to the filtrate and the solution heated at reflux for 1 hour. The solvent was removed, and the residue crystallized

from DMF. A mixture of 7- and 9-benzylguanine in a ratio of 1:7 was obtained (determined by NMR) (4.85 g, 80 %). The mixture (0.5 g) was transferred on a filter funnel filled with Celite and washed with MeOH (500-700 mL). The resulting filtrate was concentrated to provide 9-benzylguanine (0.4 g, 91%).:

m.p. >300° C, UV (H_2O, pH 6.2)λ_{max} =255 nm (ε =13300); MS (FAB) m/e =242 (MH^+, 60%); HRMS for $C_{12}H_{11}N_5O$:cal. 241.096, found 241.096 ; ^1H NMR (DMSO-d_6 δ 10.63 (1H, br.s), (7.76 (1H, s), 7.20-7.37 (5H, m), 6.45 (2H,br.s), 5.18 (2H, s).

Synthesis Example 5

N^{2-}Acetyl-9-benzylguanine

Ac_2O (2.9 mL, 0.031 mole) was added to a suspension of 9-benzylguanine (3.7 g, 0.015 mole) in 1-methyl-2-pyrrolidone (25 mL). The reaction mixture was heated at 150° C for 4 hours and the solvent removed. Fresh 1-methyl-2-pyrrolidone was then added, followed by diethylether, with vigorous stirring. The mixture was allowed to cool overnight. The resulting crystals were separated, washed with THF and dried to yield N^2-acetyl-9-benzylguanine (1.95 g, 46%).

m.p. =223-226° C, UV (H_2O, pH =7.0) λ_{max} =261 nm (ε =20900); MS (FAB) m/e =284 (MH^+=, 100%), HRMS for $C_{14}H_{13}N_5O_2$ calc. 283.108, found 283.108 ; ^1H NMR (DMSO-d_6) δ 12.03 (1H, br. s), 11.65 (1H, br.s), 8.09 (1H, s), 7.2-7.3 (5H, m), 5.32 (2H, s), 2.16 (3H, s)

Synthesis Example 6

7-(4-Hydroxy-3(hydroxymethyl)but-1-yl)guanine

N^{2-}Acetyl-9-benzylguanine (0.5 g, 1.8 mmole) was suspended in 1-methyl-2-pyrrolidone (5 mL) and 4-acetoxy-3-acetoxymethyl-1-butyl tosylate (0.76 g, 2.1 mmole) was added and heated at 120° C for 2 hours. Then additional 4-acetoxy--3-acetoxymethyl-1-butyl tosylate

(0.28g, 0.8 mmole)was gradually added, and the heating at 120° C continued for 18 hours. The reaction mixture was allowed to cool and then poured into Et_2O (20 mL). One hour later, the solvent was decanted, the residue washed with Et_2O (10 mL) and dissolved in MeOH (25 mL). Char-coal was added and the resulting mixture heated to reflux and filtered hot. Ammonium formate (0.4 g) and 10% Pd/C (0.15 g) were added to the resulting filtrate and the mixture kept at reflux for 4 hours. The mixture was then filtered and the catalyst washed with MeOH (10 mL). The solvent was removed by reduced pressure. The residue was then dissolved in 1 M NaOH (10 ml) and heated on a steam bath for 30 min. The mixture was cooled and neutralized with conc. HCl, allowed to stay for 3 hours until a white solid separated. This solid was filtered, washed with cold water and allowed to dry *in vacuo* at 60° C. White crystals were obtained (132 mg, 29%). ;

m.p. =281-283° C; UV (H_2O, pH =6.5) λ_{max} = 285 (ε =3000); MS (FAB) m/e =254 (MH^+, 90%); HRMS for $C_{10}H_{15}N_5O_3$ calc.253.118, found 253.118; ^1H NMR (DMSO-d_6) δ 10.74 (1H, br.s), 7.93 (1H, s), 6.12 (2H,br.s), 4.41 (2H, br.s), 4.23 (2H, t), 1.74 (2H, m), 1.4 (1H, m).

Synthesis Example 7

9(4-Hydroxy-3-(hydroxymethyl)but-1-yl) guanine

4-Acetoxy-3-acetoxymethyl-1-butyl tosylate (2.15 g, 6 mmole) was added to a suspension of N^2-acetyl-7-benzylguanine(1.42 g, 5 mmole) in 1-methyl-2-pyrrolidone (10 mL) and the mixture was heated for 2 hours at 120° C, then repeatedly added further 4-acetoxy-3-acetoxymethyl-1-butyl tosylate (0.36 g, 1 mmol), and reheated at 120° C for additional 2 hours. The reaction mixture was cooled and poured into Et_2O (50 mL). The solvent was decanted after 1 hour period, the residue was washed with Et_2O (10 mL) , the solvent decanted again, and the rest dissolved in MeOH (25 mL). Then, char-coal was added, the mixture was heated to boil and filtered hot. Ammonium formate (0.9 g) and 10% Pd/C (0.3 g)were added to the filtrate and the reaction mixture was heated at reflux for 4 hours, then filtered and the remaining catalyst was washed with MeOH (10 mL). The solvent was

removed under reduced pressure and the residue dissolved in 1 M NaOH solution (10 mL) and heated on a steam bath for 30 min. The reaction mixture was allowed to cool and was neutralized with conc. HCl , and then allowed to stand for 3 hours until white crystals began to separate. The solid was collected on a filter, washed with cold water and finally dried *in vacuo* at 60° C. White crystals were collected (0.6 g, 47%).;

m.p. =271-273° C; UV (H_2O, pH =5.7) λ_{max} =253 (ε =9100); MS (FAB) m/e =254 (MH^+, 62%), 185 (100%); ^{1}H NMR (DMSO-d6) δ 10.51 (1H, br.s), 7.68 (1H, s), 6.41 (2H, br.s), 4.44 (2H, br.s), 3.99 (2H, t)1.70 (2H, m), 1.45 (1H, m).

Synthesis Example 8

N^2-Acetyl-9-(4-acetoxy-3-(acetoxymethyl)but-1-yl)guanine

In a suspension of 9-(4-hydroxy-3-(hydroxymethyl)but-1-yl)guanine (1.4 g,6 mmole) in 1-methyl-2-pyrrolidone (10 mL) Ac_2O (2.4 mL, 25 mmol) was added and the reaction mixture was heated at 150° C for 5 hours. The solvent was removed under reduced pressure and the residue was dissolved in a water-MeOH 50 : 50 mixture, char-coal was added and filtered while hot. The filtrate was allowed to cool in a refrigerator for 2 hours. The separated crystals were filtered and dried to afford N^2-acetyl-9-(4-hydroxy-3-hydroxymethyl)but-1-yl)guanine (1.65g + 0.1 g from the second crop g, 83%);

m.p. = 222-223 °C; ^{1}H NMR (DMSO-d_6) δ 12.02 (1H, br.s), 11.70 (1H, br.s), 8.03 (1H, s), 4.17 (2H, t), 4.03 (4H, d), 2.20 3H,s,), 1.84-2.02 (9H, m).

Synthesis Example 9

9-(4-acetoxy-3-(acetoxymethyl)but-1-yl)-2-acetylamino-6-(2',4',6'-triisopropylbenzenesulfonyloxy)9H-purine

A mixture of N^2-acetyl-9-(4-acetoxy-3acetoxymethylbut-1-yl)guanine (1.3 g, 3.4 mmole), 4-dimethylaminopyridine (0.012 g, 1.7 mmole), triethylamine (1.9 mL , 1.4 mmol),

anhydrous dichloromethane (35 mL) and 2,4,6,-triisopropylbenzenesulfonyloxy chloride (2.08 g, 6.9 mmol) was stirred at room temperature up to a clear solution (2.5 hours). The solvent was removed and the product was isolated after purification by flash chromatography method (column prepared in CH_2Cl_2, eluted with ETA). A yellow foam was obtained (2.21 g, 99%). and was used in subsequent reactions.

MS (FAB) m/e = 646 (MH^+, 100%); ^{1}H NMR ($CDCl_3$) 8.13 (1H, b.s.), 8.02 (1H, s), 7.25 (2H, s), 4.25-4.11 (8H, m), 2.95 (1H, m), 2.37 (3H, s), 2.14-1.98 (9H, m), 1.28 (18H, d)

Synthesis Example 10

9-(4-Hydroxy-3- (hydroxymethyl)-but-1-yl)-2-aminopurine

9-(4-Hydroxy-3-(hydroxymethyl)but-1-yl-2-acetylamino-6-(2',4',6',-troiisopropylbenzenesulfonyloxy)9H-purine (8.5 g, 13.2 mmole)was dissolved in ethanol (140 mL) , catalyst 10% Pd/C (1.4 g)and triethylamine (19.8 mL), 0.14 mole)were added and the mixture subjected to hydrogenation in a Parr hydrogenator at 80-85° C (3 bar) for 8 hours. The catalyst was filtered off and washed with hot ethanol. An acetylated intermediate (3.1 g, 60%) separated first after cooling the solution. It was dissolved (2.65 g) in water (20mL) and in aqueous methylamine (40% , 9 mL). The resulting solution was then stirred for 15 min at room temperature, and evaporated and repeatedly co-evaporated with each 10 mL of water. The residue was recrystallized from ethanol to yield 9-(4-hydroxy-3-hydroxymethyl0 but-1-yl)-2-aminopurine (1.7 g, 99%).

^{1}H NMR (DMSO-d_6) δ 8.55 (1H, s), 8.07 (1H, s), 6.49 (2H, s), 4.44 (2H, t), 4.11 (2H, t) , 3.1-3.5 (4H, m), 1.76 (2H, q), 1.45 (1H, m).

Synthesis Example 11

9-(4-Acetoxy-3-acetoxymethyl)but-1-yl)-2-aminopurine

A mixture of 9-(4-hydroxy-3-hydroxymethyl)but-1-yl)-2-aminopurine (1.75 g, 7.4 mmole), Ac_2O (1.7 mL) in pyridine (1.8 mL), DMAP (90 mg, 7.4 mmole) in anhydrous THF (30 mL)was stirred for 3 hours at room temperature. The solvent was evaporated and the residue dissolved in water. This mixture was extracted with CH_2CL_2 (3x 40 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated. A white powder was isolated after the elaboration of the mixture with Et_2O and with subsequent filtration to provide famciclovir (2.3 g,97%).

^{1}H NMR (DMSO-d_6) δ 8.56 (1H, s), 8.9 (1H, s), 6.49 (2H, s (, 4.13 (2H, t), 4.02 (4H, d), 1.99 (6H, s), 1.87 (3H, m).

Synthesis Example 12

N^2-Acetyl-7-benzyl-(4-acetoxybut-1-yl)guaninium bromide

4-Bromobut-1-yl acetate (10.7 g, 0.055 mole)was added to a suspension of N^2-acetyl-7-benzylguanine (14.1 g,0.05 mole) in 1-methyl-2-pyrrolidone (35 mL). The reaction mixture was heated for 2 hours at 120° C. The mixture was then cooled down and 500 mL of ETA was added. The precipitate was collected by filtration after 1 hour period, the obtained white salt was washed with acetone and dried to obtain N^2-acetyl-7-benzyl-9-(4-acetoxybut-1-yl)guaninium bromide (21 g, 88%), which was used without further purification.

^{1}H NMR (DMSO-d_6) δ 12.60 (1H,br.s), 12.17 (1H, s), 9.83 (1H, s), 7.4-7.5 (5H, m), 5.72 (2H, s), 4.29 (2H,t), 4.04 (2H, t), 2.23 (3H, s), 2.01 (3H, s), 1.85 (2H, m), 1.67 (2H,m).

Example 13

9-(4-Acetoxybut-1-yl)guanine

A mixture of N^2-acetyl-7-benzyl-9-(4-acetoxybut -yl)guaninium bromide (21 g, 0.044 mole), ammonium formate (7 g,0.11 mole) in methanol (400 mL) and 10% Pd/C (2.7 g) was heated at reflux for 4 hours, then filtered hot and the remaining catalyst was washed with hot water (50 mL). The filtrate was heated at reflux for an additional hour, then evaporated at reduced pressure, and the residue was crystallized from water to afford pure 9-(4-acetoxybut-1-yl)guanine (7.7 g, 66%). m.p. = 215-216 °C; ^{1}H NMR (DMSO-d_6) δ 10.54 (1H, s), 7.70 (1H, s), 6.44 (2H, br.s), 3.97 (4H, m), 1.99 (3H, s), 1.77 (2H, m), 1.52 (2H, m).

Synthesis Example 14

N^2-Acetyl-9-(4-acetoxybut-1-yl) guanine

To a suspension of 9-(4-acetoxybut-1-yl) guanine (3.0 g, 0.01 mole) in 1-methyl-2-pyrrolidone (10 mL), Ac_2O (2.1 mL, 0.02 mole)was added and the mixture was heated at reflux for 5 hours. The reaction mixture was cooled and concentrated to approximately 8 mL of volume. Et_2O (50 mL) was added with stirring, then cooled and the resulting crystals collected on a filter and washed with Et_2O. After drying, N^2-acetyl -9-(4-acetoxybut-1-yl)guanine (3.16 g, 91%) was obtained. and could be used in subsequent steps without further purification.; m.p. =215-218° C; MS (ES) m/e = 307 (M^+, 100%); ^{1}H NMR (DMSO-d_6) δ 12.03 (1H, br.s), 11.71 (1H,br.s), 8.01 (1H, s), 4.09 (2H, t), 4.01 (2H, t), 2.18 (3H, s), 2.00 (3H,s), 1.83 (2H,m), 1.55 (2H, m).

Example 15

N^{2-}Acetyl-9-benzyl-7-(4-acetoxybut-1-yl)guaninium bromide

4-Bromobut-1-yl acetate (2.9 g, 0.015 mole) was added to 9-benzylguanine (2.4 g,0.01 mole)in 1-methyl-2-pyrrolidone (20 mL). The suspension was heated at 120° C for 2 hours. Et_2O (200 mL)was added to the cooled solution. After a while (1 hour), the solvent mixture was decanted from a dark coloured gummy residue, which was further elaborated with ETA to provide a salt. This solid was then filtered and washed with ETA. After drying, N^2-acetyl-9-benzyl-7-(4-acetoxybut-l-yl) guaninium bromide (4.3 g, 99%) was obtained and it was used in following experiments without further purification. ^{1}H NMR (DMS)-d_6) δ 11.70 (1H, s), 9.44 (1H, s), 7.41 (5H, m), 7.25 (2H, br.s), 5.38 (2H, s), 4.40 (2H, t), 4.02 (2H, t), 1.90 (2H, m), 1.62 (2H, m).

Example 16

7-(4-Acetoxybut-1-yl) guanine

A mixture of 9-benzyl-7-(4-acetoxybut-1-yl) guninium bromide (4.3 g, 0.01 mole), ammonium formate (1.9 g, 0.03 mole), and Pd/C (0.4 g)in methanol (80 mL) was heated at reflux with stirring for 4 hours, then filtered hot, and the filtrate evaporated to dryness under reduced pressure. The catalyst was washed with hot 2 M NaOH solution (30 mL) and this solution was added to the residue. The mixture was then heated on a steam bath for 20 min and neutralized with conc. HCl. After 1 hour, the formed crystals were collected and washed with water, and thoroughly dried to yield : 7-(4-acetoxybut-1-yl)guanine (1.55 g, 71%). ; ^{1}H NMR (DMSO-d_6) δ 10.76 (1H, br.s), 7.91 (1H, s), 6.12 (2H, br.s), 4.44 (1H, t), 4.18 (2H, t), 3.37 (2H,t), 1.99 (3H, s), 1.78 (2H, m), 1.35 (2H, m).

Synthesis Example 17

N^2-Acetyl-7-(4--acetoxybut-1-yl)guanine

7-(4-Acetoxybut-1-yl)guanine (1 g, 4 mmole) was acetylated in a suspension of 1-mehyl-2-pyrrolidone (10 mL), after the addition of Ac_2O (1.1 mL, 11 mmole) and heating at reflux for 10 hours. The solvent was removed at reduced pressure, the was treated with ETA (5 mL) and the solid separated by filtration. Solid was then washed with acetone and dried to provide N^2-acetyl-7-(4-acetoxybut-1-yl)guanine (1.05 g, 90%).; MS (ES) m/e = 307 (M^+, 100%) ^{1}H NMR (DMSO-d_6) δ 12.05 (1H, br.s), 11.58 (1H, br.s), 8.19 (1H, s), 4.30 (2H, t), 4.00 (2H, t), 2.16 (3H,s), 1.98 (3H, m), 1.51 (2H, m).

Example 18

7-(4-Acetoxybut-1-yl)-2-acetamino-6-(2',4',6',-triisopropylbenzenesulfonyloxy)-7H-purine

A mixture of N^2-acetyl-7-(4-acetoxybut-1-yl)guanine (0.5 g, 1.6 mmole), triethylamine, (0.9 mL), 6.4 mmol) and 4-dimethylaminopyridine (10 mg, 0.1mmoles in anhydrous CH_2CL_2 (20 mL) and 2',4',6',-triisopropylbenzenesulfonyl chloride (1 g, 3.3 mmole) was stirred at room temperature until the solution cleared up. The solution was washed 2 times with each 15 mL portion of water. The water phase was then washed with 20 mL CH_2Cl_2. The joint organic phases were washed with brine (2x25 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, the product isolated by "flash" chromatography and processed. (CH_2Cl_2-300 mL; ETA-600 mL), to obtain 7-(4-acetoxy-1-yl-2-acetylamino-6-(2',4',6'-triisopropylbenzenesulfonyloxy)7H-purine. (0.9g, 96%) as a yellow foam.; ^{1}H NMR (DMSO-d_6) δ 8.14 (1H, s), 7.62 (1H, s), 7.27 (2H, s), 4,42 (2H, t), 4.14 (2H,t), 4.06 (2H, m), 2.97 (1H,m), 2.12 (3H, s), 2.07 (3H, s), 1.73 (2H,m), 1.63 (2H, m)1.30 (6H,d), 25 (12H, d).

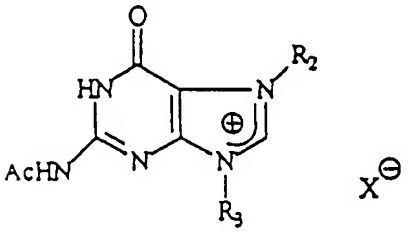
Synthesis Example 19

7-(4-Acetylbut-1-yl)-2-acetylamino-7H-purine

7-(4-acetoxybut-1-yl)-2-acetylamino-6-(2',4',6'-triisopropylbenzenesulfonyloxy)7H-purine (0.55 g, 1 mmole) was dissolved in ethanol (25 mL), then were dded 10% Pd/C (0.2 g) aand triethylamine (0.15 mL, 1.1 mmole). Hydrogenation was performed in a Parr hydrogenation apparatus at 75° C and 3 bar pressure. After 6 hours, the catalyst was removed by filtration and washed with hot ethanol. A mixture of N^2-acetyl-7-(4-acetoxybut-1-yl)guanine and 7-(4-acetoxybut-1-yl)-2-acetylamino-7H-purine was obtained. The products were separated by flash chromatography (CH_2Cl_2 : MeOH = 20:1; 400 mL ; and 10:1, 400 ml) to obtain 7-4-acetoxybut-1-yl)-2-acetylamino-7H-purine (0.14 g, 50%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.42 (1H, br. s), 9.10 (1H, s), 8.62 (1H, s), 4.35 (2H, t), 4.01 (2H, t), 2.18 (3H, s), 1.98 (3H,s), 1.89 (2H, m), 1.54 (2H,m).

PATENT CLAIMS

1. A process for preparing compounds of the formula 4 or 5:



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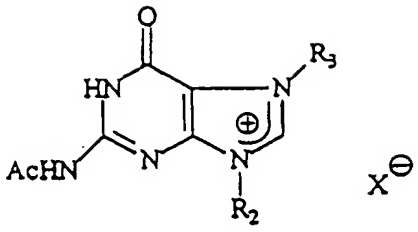


5

wherein:

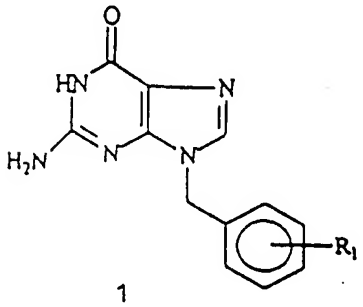
Ac represents acetyl,

R_2 represents a C_1-C_{12} linear or branched, saturated or unsaturated alkyl group, that may contain a 3-7 membered ring in the molecule, and also an ether, thioether, acetal, thioacetal, lactone, thiolactone, mono- or diacyl group, phosphorylmethoxy, phosphorylethoxy and phosphate groups,

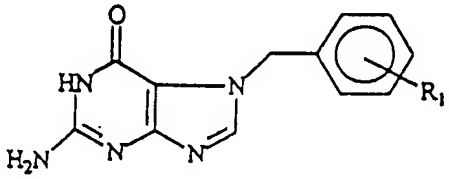
R_3 represents ring substituted p-methoxy, p-nitro, p-methyl benzyl groups,

X represents chloro, bromo, iodo, p-toluene sulphonic groups or mesyloxy groups;

characterized in, that a compound represented by the formula 1 or 2



1



2

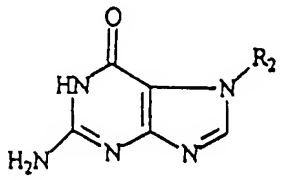
wherein R_1 represents hydrogen, a C_1-C_6 alkyl group, a C_1-C_{16} alkoxy group, a hydroxy group, a nitro group, an amino group, fluoro, chloro, bromo or iodo,

is reacted with the compound representing the desired substituent (chain) with the reactive removable group, represented by the formula 3

R_2X 3

wherein X and R_2 have the above meanings.

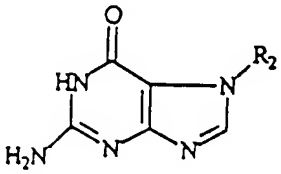
2. A compound of the formula 6



6

wherein R_2 has the meaning defined in claim 1.

3. A process for preparing 9 and 7 substituted purine derivatives of formulae 6 and 7



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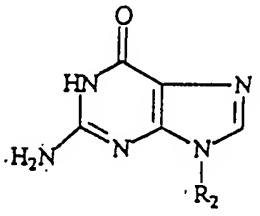
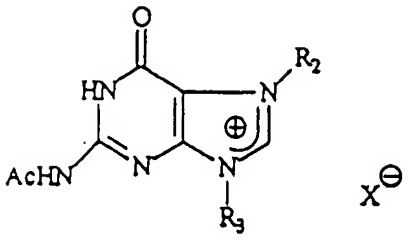


7

wherein R_2 has the above meanings,

by hydrogenation of the above compounds of formulae 4 and 5.



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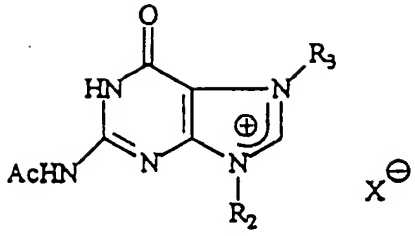

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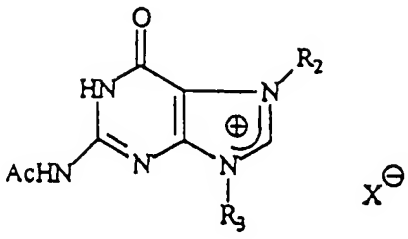
wherein Ac, X, R_2 and R_3 have the meanings defined in claim 1.

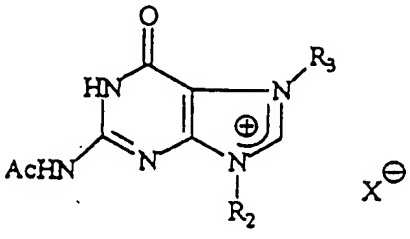
4. Compounds of formula 4



4

wherein Ac, X, R_2 and R_3 have the meanings defined in claim 1.

5. Compounds of formula 5



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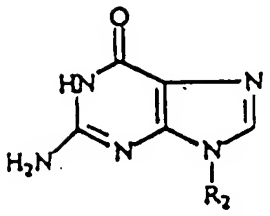
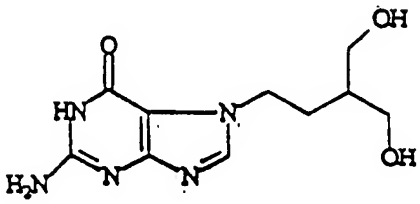
wherein Ac, X, R_2 and R_3 have the meanings defined in claim 1.

6. A process as claimed in claim 3, characterized in, that it yields penciclovir of the formula

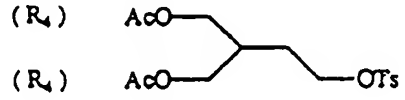


and the N7 isomer thereof represented by the formula 10



10

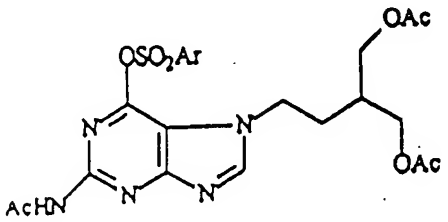
7. A process as claimed in claim 1, 3, 6, characterized in, that the chain R_2X is represented by the formula 9



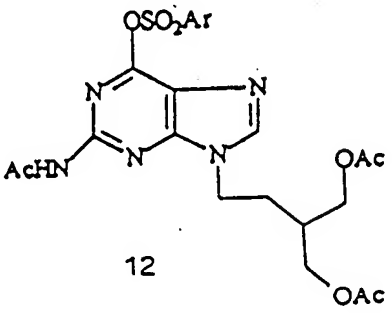
9

wherein R_4 represents a C_1-C_8 acyl group, a C_1-C_{10} alkyl group or a C_7-C_{22} arylalkyl group.

8. A process for the deoxygenation of the compounds of formulae 6 and 7, defined in claim 3, characterized in, that it is performed *via* the O6-sulphonylated intermediates 11 and 12



11



12

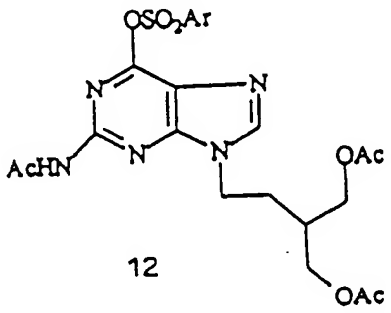
wherein

Ac represents acetyl,

Ar represents 2,4,6-$^{i}Pr_3C_6H_2$-, 2,4,6-$Me_3C_6H_2$-, 4-MeC_6H_4-, 4-FC_6H_4-,

into the famciclovir of the formula 14 and the isomer thereof of the formula 13

9. Compounds of formula 12

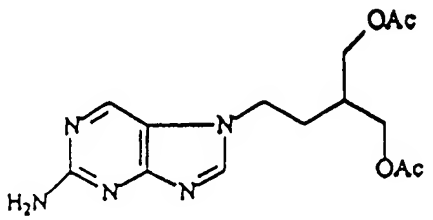


12

wherein Ac has the meaning defined in claim 1, Ar has the meaning defined in claim 8.

10. A compound of formula 13

{7-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-7H-purine}



13

wherein Ac has the meaning defined in claim 1.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/SI 99/00021

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D473/00 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 728 757 A (AJINOMOTO KK) 28 August 1996 (1996-08-28) cited in the application	1-10
X	the whole document	1,4,5

Y	KJELLBERG J ET AL: "STUDIES ON THE ALKYLATION OF DERIVATIVES OF GUANINE" NUCLEOSIDES & NUCLEOTIDES,XX,XX, vol. 8, no. 2, page 225-256 XP000616145 ISSN: 0732-8311 cited in the application the whole document	1-5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1999	21/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. ...nal Application No
PCT/SI 99/00021

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Interr. ...nal Application No
PCT/SI 99/00021

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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